

## REMARKS

Applicant respectfully requests reconsideration. Claims 28, 29, 31-33 and 36 are pending in this application. No claim is amended or cancelled herein. No new matter has been added.

### Rejection Under 35 U.S.C. 103

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al. 1992 Jpn J. Center Res Vol. 83 pgs. 1128-1131, in view of Goodchild et al. 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al. US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al. US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994).

The Office maintains its rejection that it would have been prima facie obvious for one of ordinary skill in the art to combine the teachings of Kuramoto et al., Goodchild et al., Hutcherson et al. and Cheng et al. to arrive at the instant claims. Applicant respectfully disagrees and requests reconsideration of this rejection. The Office continues to dismiss Applicant's arguments without addressing all the rebuttal arguments and evidence presented by Applicant. A person of ordinary skill in the art would not have been motivated to modify the ODN of Kuramoto et al. by adding phosphorothioate internucleotide linkages as taught by Goodchild et al. or Hutcherson et al. because of the unpredictability of phosphorothioate linkages as evidenced by the references previously cited by Applicant. The combination would only have been effected using hindsight reasoning as discussed below.

Furthermore, the Office has refused to consider the Declaration of Dr. Cy Stein and asserted that the Declaration is not relevant to the issue of non-obviousness of the claimed subject matter because it "include(s) statements which amount to an affirmation that the affiant has never seen the claimed subject matter before." Office Action at page 4. Applicant respectfully disagrees. The Declaration of Dr. Cy Stein was prepared in connection with an Interference involving an application which derives priority from the same patent application to which the instant patent application claims priority, US 08/386,063. Moreover, the declaration is presented to the Office solely as evidence of the unpredictability of phosphate modifications in oligonucleotides.

Applicant has presented the Declaration of Dr. Cy Stein as further confirmation by a person of skill in the art of the unpredictability of phosphate backbone modifications. Dr. Cy Stein has studied oligonucleotide backbone modifications for more than 17 years and has more than ordinary skill in the particular field of phosphate modified nucleic acids. Whether Dr. Cy Stein has seen the instant claims is irrelevant, as the objective of his Declaration was to highlight the unpredictability of phosphate modifications on immunostimulation at the relevant time frame of 1994-1996. In his Declaration, Dr. Cy Stein states that phosphate backbone modification were known to have unpredictable and undesirable effects on nucleic acids. Dr. Cy Stein further states that among the complications introduced by phosphorothioate modification is the creation of stereochemistry, and that one of skill in the art would not have known whether the introduction of stereochemistry would affect the immunostimulation of nucleic acids. Accordingly, in the absence of the work of the instant invention, it would not have been known at the time of the invention whether a phosphorothioate bond would substantially alter the shape of the oligonucleotide so as to destroy immunostimulatory ability.

It is further stated in the Office Action that the skilled artisan would have modified the ODN disclosed by Kuramoto et al. by adding phosphorothioate linkages based on the teachings in Hutcherson et al. of a method of administering phosphorothioate oligonucleotide analogs which produce a localized immune stimulation and for enhancing the efficacy of antiinfective and anticancer agents. Applicant respectfully disagrees and maintains that the teachings found within the references themselves would not have led the skilled artisan to the combination. Kuramoto et al. teach that the immunostimulatory DNA is representative of immunostimulatory bacterial DNA. Bacterial DNA is not phosphorothioate modified. Kuramoto et al. further teaches that the immunostimulatory activity of the ODN is due to the hexameric palindrome within the sequence. In contrast, Hutcherson et al. does not provide any teachings regarding inclusion of a palindrome within the sequence. In fact, Hutcherson et al. indicates that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity. Thus, Hutcherson et al. is describing molecules that are distinct from Kuramoto et al. and contain phosphorothioate modifications and do not require palindromes.

Given the teachings of Kuramoto et al. and Hutcherson et al., the skilled artisan would have expected that the molecules of Kuramoto et al. and Hutcherson et al. are operating through different mechanisms. In the absence of any knowledge regarding the mechanisms through which these nucleic acids achieve immune stimulation, it would have been both undesirable and unpredictable to modify the ODN of Kuramoto et al. as taught by Hutcherson et al. Furthermore, in light of the known unpredictability of the phosphorothioate modifications it would not have been known at the time of the invention whether a phosphorothioate bond would substantially alter the shape of the oligonucleotide so as to totally destroy immunostimulatory ability. As stated by Dr. Cy Stein in his Declaration, among the complications introduced by phosphorothioate modification is the creation of stereochemistry at each site with a phosphorothioate bond, creating distinct versions of the molecule. The two stereochemical forms of the phosphorothioate linkage each produce molecules with biological activities that can be distinct from each other, and distinct from an unmodified nucleic acid, having the same base pairs. This stereochemistry of phosphorothioates was known prior to 1994, and one of skill in the art would not have known whether the introduction of stereochemistry would affect immunostimulation.

Thus, in view of the different teachings between Kuramoto et al. and Hutcherson et al. and the expected different mechanisms of action as well as the unpredictability of phosphorothioate bonds, the skilled artisan would not have combined the teachings in the absence of hindsight.

All rebuttal arguments and evidence presented by Applicant must be considered by the Office. MPEP 2141 and 2145. The CAFC has repeatedly held that it is an error not to consider rebuttal evidence presented to counter a rejection. *In re Sullivan* Case No. 2006-1507, (Fed. Cir., Aug 29, 2007); *Sud-Chemie, Inc v. Multisorb Technologies, Inc.*, Case No. 2008-1247, (Fed. Cir., Jan 30, 2009). Applicant presented prior references that demonstrate the unpredictability of phosphorothioate linkages, which have not been suitably addressed by the Office. The Office asserts that Applicant's arguments were addressed in the prior Office Action dated 9/12/2008 on pages 4-14. Applicant respectfully disagrees.

In the cited Office Action, the Office has noted that several references have been listed in response to the Office Action; however, the Office has failed to adequately address the teachings presented in the references. Applicant presented a 1993 Science paper by Stein et al. (Science v.

261 p. 1004 1993) which shows that phosphorothioate modifications can have unpredictable effects on an oligonucleotide. In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. Phosphorothioate modifications have many more biological effects than simply reducing oligonucleotide degradation *in vivo*. As detailed in Stein et al., those effects were not well understood. For example, at p. 1008, col. 3 and p. 1009, cols. 1 and 2, four possible explanations for the non-specific antisense effects of a particular phosphorothioate antisense oligonucleotide are described. Additionally Perez et al. (PNAS v. 21, p.5597-5561, 1994) teaches that one should use caution when considering oligonucleotides with phosphorothioate backbones because of the danger of nuclear transcription factor induction. The Examiner has not addressed these teachings of the cited references which clearly highlight the unpredictability of phosphorothioate modifications. In light of these teachings, the skilled artisan at the time the invention was made would not have been motivated to alter the ODN of Kuramoto et al. to include a backbone modification as taught by Goodchild et al. or Hutcherson et al.

Applicant requests the Examiner to appropriately address the presented rebuttal arguments and evidence, or to withdraw the rejection.

#### **Double Patenting**

Claims 28-29, 31-33 and 36 have been provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 19 and 21 of copending Application No. 10/956,745 in view of Oberhauser et al. 1992 Nucleic Acids Research vol. 20 p. 533-538 and Hutcherson et al. US 5,723,335 1998 (continuation of serial no. 217,988, March 25, 1994) and Sonehara et al. (J. Interferon and Cytokine Research, 1996, 16:799-803).

The rejection is a provisional one since claims 19 and 21 in the 10/956,745 application have not been found allowable. If the cited claims are found allowable, Applicant will address the rejection.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70083US07.

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Respectfully submitted,

By 

Helen C. Lockhart  
Registration No.: 39,248  
WOLF, GREENFIELD & SACKS, P.C.  
Federal Reserve Plaza  
600 Atlantic Avenue  
Boston, Massachusetts 02210-2206  
617.646.8000